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GUEST EDITORIAL

Pap Smears: Interpreting the New Bethesda Terminology

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HISTORICAL INTRODUCTION AND PREVIOUS REPORTING SYSTEMS

The idea of diagnosing cancer through the recovery and identification of exfoliated cancer cells in body fluids and secretions dates back to the nineteenth century. The "Father of Exfoliative Cytology," George Papanicolaou, was born in Coumi, Greece, received his M.D. degree from the University of Athens (1904) and his Ph.D. degree from the University of Munich (1912). He came to the United States and was associated with Cornell University College of Medicine from 1914 until his death in 1962. Initially, Papanicolaou studied cells exfoliated from the vaginal epithelium of guinea pigs. He explored cytologic changes in the vaginal fluid of rodents and then applied the techniques to the human female to study the sex cycle and reproductive function. Having established a satisfactory technique for examination of vaginal smears, Papanicolaou began to apply this to diagnose uterine cancer between 1923 and 1928 and first presented his findings in 1928 at the Third Race Betterment Conference. About the same time there was a well-illustrated publication with similar findings by Babes [1]. Papanicolaou, however, was fortunate enough to work closely with clinicians Herbert Traut and Andrew Marchetti and to have the support and encouragement of the Dean of the Cornell Medical College, Joseph C. Hinsey, in his work during the 1930s, a period when other pathologists were paying more attention to examination of cells in various fluids. Such support and encouragement were most important in the development and use of the Pap smear. Papanicolaou first reported vaginal smear findings in an obstetrics/gynecology journal in 1941, and subsequently, a comprehensive monograph was published [2]. Close cooperation between anatomist (later pathologist) and clinician was the basis for the success of the Pap smear as a diagnostic tool. Consideration of findings in the vaginal smears (later including cervical/endocervical) led to Papanicolaou suggesting the following groups: Class I, absence of atypical or abnormal cells; Class II, atypical cytology but no evidence of malignancy; Class III, cytology suggestive of, but not conclusive for, malignancy; Class IV, cytology strongly suggestive of malignancy; and Class V, cytology conclusive for malignancy. Although this remained the basis for classification for many years, there were often simplifications intended to mean the same, but considered "better" because they were more concise. They are Class I, benign; Class II, atypical benign; Class III, suspicious; Class IV, probably malignant; and Class V, malignant.

The first-generation Papanicolaou trainees had fairly uniform ideas, but as more cytologists and pathologists (and in the early days gynecologists who learned to interpret Pap smears and often established and ran the diagnostic laboratories) enbraced the technique, the method of reporting varied. Some pathologists [3] developed and advocated terminology using diagnostic terms, such as mild, moderate, and severe dysplasia, carcinoma in situ (CIS), and invasive carcinoma. Others [4] proposed and adopted the term "cervical intraepithelial neoplasia" (CIN), the categories of which (CIN 1, 2, 3) corresponded to mild, moderate, and severe dysplasia/CIS, respectively. As long as a clinician stayed in one place and was associated with one group of pathologists, there was no major problem.

THE BETHESDA REPORTING SYSTEM

With variation in terminology among different groups and with the mobility of medical people, problems developed and a committee was formed. The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses was developed at a National Cancer Institute (NCI)-sponsored workshop in December 1988, to provide uniform diagnostic terminology that would facilitate communication be-

Table I. Simplified Comparison of Diagnostic Systems for Pre-Invasive Cervical Squamous Neoplasia

4-Tier[3]	3-Tier[4]	The Bethesda System[5]
mild dysplasia	CIN I	LGSIL
moderate dysplasia	CIN II	HGSIL
marked or severe dysplasia carcinoma in situ	CIN III	

CIN = cervical intraepithelial neoplasia
LGSIL, HSGIL = low grade and high grade squamous intraepithelial lesions, respectively

tween the laboratory and the clinician [5]. A second workshop was held in 1991 and amendments and modifications made where needed. An excellent summary of this new system is available and recommended [6]. It has good illustrations, is easy to read, and is inexpensive. Reading the text and looking at the illustrations should make interpretation of reports much simpler. A comparison of recent diagnostic systems is useful (Table I).

SPECIMEN ADEQUACY

Specimen adequacy is based upon four elements. The first is patient and specimen identification. That means that the clinician should use a foolproof way of labeling the smear and making certain that it is accompanied by the correct request sheet. The second element is pertinent clinical information. Without it, an adequate interpretation may be impossible. For the clinician to receive the most useful report, he or she should provide pertinent clinical information, including age, menstrual data, current complaint, and relevant past history including any surgical procedure, or radiation therapy involving the cervix, or chemotherapy. Previous relevant Pap smear findings should be included. The third element is technical interpretability. Excessive blood and thick inflammatory exudate may conceal groups of cells so that their interpretation is impossible. The fourth element is cellular composition and sampling of the cervical transformation zone (presuming that the uterus is still in place, but this should have been clarified under pertinent clinical information). If the above four elements are included, the statement of adequacy, which is part of the pathologist's report, is marked as satisfactory. If some elements are missing or inadequate, the statement is designated as satisfactory-limited accompanied by an explanation. Unsatisfactory is applied when the cytopathologist considers that he or she cannot interpret a scanty or thick or overstained smear. If there are some questionably "atypical" cells, they should be reported, although there is not general agreement whether such a smear should be reported as satisfactory-limited or unsatisfactory.

DIAGNOSTIC CATEGORIES

Next come the descriptive diagnoses. Fortunately, there is a negative category. There are benign cellular changes, which include infection and these would be listed (e.g., Trichomonas vaginalis, cellular changes associated with herpes simplex virus). They also include reactive changes associated with inflammation, atrophy with inflammation, radiation, and those related to an intrauterine device (IUD). With the latter, Actinomyces may be identified.

Epithelial cell abnormalities include a wide spectrum of changes. First are the squamous cells.

1. Atypical squamous cells of undetermined significance (ASCUS). The pathologist may suggest what he or she believes is the most likely explanation, but ordinarily this identification means that they are not definitely dysplastic/neoplastic.
2. Low-grade squamous intraepithelial lesion (originally LGSIL, but more recently designated LSIL). This includes mild dysplasia (CIN1) and koilocytosis, koilocytotic atypia, and condylomatous atypia. The latter three are now reported as human papilloma virus (HPV) effect.
3. High-grade squamous intraepithelial lesion (formerly HGSIL, now HSIL). This includes moderate dysplasia (CIN2) and severe dysplasia/carcinoma in situ (CIN3). There is not uniform agreement among cytopathologists that moderate dysplasia should be in the same category as severe dysplasia.
4. Squamous cell carcinoma.

Then, there are glandular cells. These are categorized as follows: endometrial cells cytologically benign in the postmenopausal woman, atypical glandular cells of undetermined significance (AGCUS or more recently AGUS), endocervical adenocarcinoma, endometrial adenocarcinoma, adenocarcinoma suggesting an extrauterine site of origin, and adenocarcinoma, not otherwise specified (NOS). Other malignant cells are less commonly found, e.g., suggestive of sarcoma, but should also be noted in the report.

FOLLOW-UP OF NEGATIVE AND ABNORMAL REPORTS

The negative smear has routine follow-up unless there is a history of a prior atypical smear, and then there may be some modification. With a report of infection, this may be treated. Additional treatment may be considered if Actinomyces is found in a patient with an IUD in place. The ASGUS and the AGUS smears may be repeated in 3–6 months depending on past history, family history, and patient's request. If the clinician has noted a cervical lesion that might be cancer and possibly the site of origin

of the equivocal cells, obviously such should be biopsied. If he or she is very suspicious, the Pap smear (especially if not entirely satisfactory), may be repeated sooner than 3 months bearing in mind that a negative smear taken so soon after the other is not necessarily valid.

Those with a low-grade squamous intraepithelial report (LSIL) do not at this time have an unquestionably correct method of management. Certainly, the smear should be repeated in 3–6 months, and there should be careful clinical examination. Currently, there is a major National Institutes of Health study under way with several management arms to determine exactly how such patients should be managed. Of course, there are various factors that may influence the method of management, including the patient's apprehension and a strong family history of neoplastic disease. With an "abnormal" report (HSIL or more atypical) obvious lesions should be biopsied. Otherwise colposcopic evaluation of the cervix (and vagina) is preferable with biopsy where indicated. A recent publication [7] gives additional information about evaluation and management options. Evaluation of glandular cells is made from biopsy or curettage specimen. When endocervical curettage and endometrial curettage are done, specimens should be submitted separately; an understanding should be reached beforehand with the pathologist as to how these specimens are best submitted. Obviously, if the adenocarcinoma found in the smear suggests an extrauterine origin, clinical evaluation beyond the uterus is indicated.

The clinician may want some clarification of the pathologist's report and may ask, "Tell me what you really mean," or may visit the laboratory to look at the cells. With some explanation by the pathologist, this may help in the clinical management. Preferably any tissue sampled should be sent to the same laboratory, as was the Pap smear, so that the pathologist interpreting the biopsy may correlate the two specimens. It is helpful to include the Pap smear number with such a biopsy. If additional biopsy material or tissue from a definitive surgical procedure is obtained, it should be reviewed with the prior material at the initial laboratory or the earlier material should be sent to the current laboratory (if different) for correlation and the benefit of the current patient and for quality control for the cytopathologist. The pap smear is another illustration how good clinician-pathologist cooperation is the basis of good patient management.

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